The Muscle Anabolic Threshold Concept for an Adapted and Efficient Nutrition during Catabolic States

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Impact of muscle loss in health and diseases

Muscle loss

- Higher risk of falls
- Muscle Weakness
- Reduction of physical Activity

↓ Energy Expenditure
- Fat oxidation
- Visceral and tissue lipid accumulation
- Insulin Resistance

AA

Immunity

Frailty, Loss of Autonomy

↑ Morbidity, ↑ Mortality
Protein metabolism

Protein Synthesis

Amino acids

Proteolyis

Bioavailability of dietary amino acids

Anabolic factors (Insulin)
Protein metabolism

Post-absorptive

Postprandial

Food intake

Anabolic response
(Gain of muscle proteins)

Catabolism
(Loss of muscle proteins)

Post prandial protein gain should compensate the post absorptive loss of proteins
In situations of muscle mass loss

Impaired anabolic response to food intake (with the RDA)

Anabolic resistance

Post prandial Protein metabolism
The Anabolic Threshold Concept

Anabolic factors
(Amino acids)

Food intake

Time

Anabolic response
Intensity

Duration of the anabolic response

Anabolic threshold to reach

The Anabolic Threshold Concept

Anabolic response Intensity

Duration of the anabolic response

Anabolic threshold to reach

Increase of the Anabolic threshold to reach

Anabolic response Intensity

Duration of the anabolic response

Anabolic response Intensity
Protein metabolism in anabolic resistance situations

Anabolic response (Gain of muscle proteins)

Post-absorptive

Food intake

Postprandial

Catabolism (Loss of muscle proteins)

Post prandial protein gain does not compensate the post absorptive loss of proteins = Muscle Atrophy
The Anabolic Threshold Concept

Anabolic response

Intensity

Increase of the Anabolic threshold to reach

Duration of the anabolic response

Increased Anabolic response Intensity

Anabolic response

Intensity

Increase of the Anabolic threshold to reach

Duration of the anabolic response
In situations of muscle loss and anabolic resistance:

Is Leucine capable to overcome the increase of muscle anabolic threshold?

3 contrasted situations
Cancer cachexia
Sarcopenia (aging)
Immobilization/bedrest
Leucine = a signal nutrient

Leucine

Rheb
Gbl.mTOR.raptor

p70S6K
(S6K1)

rp6

eIF4E

4E-BP1

Protein Synthesis
Free Leucine supplementation

Improvement of nitrogen balance
Daily et al. 1983

Improvement of body weight
Tayek et al. 1986

4 g of leucine  29 months
Improvement of muscle strength
Poon et al. 2004

8.7 g to 14.6 g leucine/kg dietary proteins in the diet
Improvement of muscle mass
Peters et al. 2011

1 g /kg body weight
Improve muscle protein synthesis
Improvement of muscle mass
Eley et al. 2007
Free Leucine supplementation in a meal

Sarcopenia and aging

Anabolic resistance

(Mosoni et al, 1995)
Leucine, Sarcopenia and Aging

Rieu et al, 2006
Katsanos et al. 2006

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**Graph:**
- **X-axis:** Time (min)
- **Y-axis:** Plasma Leucine
- **Legend:**
  - Purple: Control
  - Red: Leucine

**Bar Chart:**
- **X-axis:** Control, Leucine
- **Y-axis:** Protein synthesis
- **Note:** +57%

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Leucine, Sarcopenia and Aging

6-10 months
4.5% leucine in the diet

Negative on muscle mass
(Zeanandin et al. 2012)
Vianna et al. 2011

3 months
7.5 g leucine / day

Negative on muscle mass and strength
(Verhoven et al. 2009):
Leucine, Muscle loss and Bed rest/Immobilization

Free Leucine supplementation

3.1g leucine, 28 days:
Improvement of post prandial muscle protein synthesis
No change in muscle mass loss
Paddon-Jones et al. 2004

3.6g leucine, 60 days:
No change in muscle mass loss
Trappe et al. 2007

3.6g leucine, 60 days:
No change in muscle strength
Trappe et al. 2008

4.5% leucine in the diet
No change in muscle mass recovery
Magne et al. 2012

Post-prandial Stimulation of Muscle Protein Synthesis (% /h)

(Glover at al. 2008)
Why free leucine can be disappointing?

+ Leucine

Digestion time

20 amino acids

Muscle protein synthesis

Leucine

Increased Anabolic Threshold

Other Amino acids

Increased

Why free leucine can be disappointing?
Why free leucine supplementation disappointing?

Anabolic response intensity

Duration of the anabolic response

Increase of the Anabolic threshold to reach

Leucine signal

Amino acid availability

Duration of the anabolic response

Leucine supplementation

Increased Anabolic response intensity

Anabolic response intensity
Synchronization possible with leucine rich proteins rapidly digested

Whey Proteins
Leucine supplementation with whey

Muscle Recovery Post-immobilization

Post prandial Protein Synthesis

- Control
- + Leucine
- Whey

Magne et al. 2012

Muscle mass gain (mg)

Days of recovery
Leucine supplementation with whey

Sarcopenia and Aging

Protein Synthesis

- Controls
- Whey

Dangin et al., 2002, 2003; Boirie et al, 1997

Rieu et al, 2007
Mosoni et al. 2013

Muscle mass (10 d or 6 months)
When Resynchronisation remained inefficient?

Duration of the anabolic response?

- Decrease of the anabolic threshold
- Increase more the protein intake
- Interaction between protein and energy intake
When Resynchronisation is inefficient?

Anabolic response

Intensity

Increased

Anabolic response
Intensity

Duration of the anabolic response

Leucine signal

Amino acid availability

Decrease the anabolic threshold

Duration of the anabolic response

Anabolic response Intensity

Leucine signal

Amino acid availability

Resynchronisation is inefficient?
When Resynchronisation is inefficient?

- Increased Anabolic response Intensity
- Amino acid availability
- Duration of the anabolic response

- Leucine signal

Decrease of the anabolic threshold
How to decrease the anabolic threshold?

Most of the situations of muscle loss are associated with an increase of:

**Inflammation** and **Oxidative Stress**

- Inflammation
- Oxidative Stress
- Cytokines TNFα, IL1, IL6
- O2
How to decrease the anabolic threshold?

**Rutin, vitamin E, vitamin A, Zn et Se for 7 weeks**

Marzani et al. J Nutr 2008  
Mosoni et al. Nutrition, 2010

**Protein synthesis (%/d)**

- Aged
- Aged + Antioxidants

**Leucine concentration**

0 100 200 300 400 µM

**Muscle Mass (g)**

CT: 3.8  +10.6%  Ibuprofen

**Protein synthesis (%/d)**

Postabsorptive  
Postprandial

Marzani et al. J Nutr 2008  
Mosoni et al. Nutrition, 2010

**Protein synthesis (%/d)**

- No Inf
- Low Grade Inf
- + Ibuprofen

Rieu I, J Physiol 2009  
Balage et al. JNB, 2010
When Resynchronisation is inefficient?

- Increased Anabolic response Intensity
- Leucine signal
- Amino acid availability
- Duration of the anabolic response

**Duration of the anabolic response?**

Increase more the protein intake?
High protein diet: The protein pulse feeding?

Increase of dietary protein intake

Anabolic factors (Amino acids)

Food intake

Post prandial time

Arnal et Mosoni 1999, 2000, 2002
Anabolic response intensity

Duration of the anabolic response

Increase of the dietary protein intake

Anabolic factors (Amino acids)

Food intake

Postabsorptive concentrations

Time

The protein pulse feeding?

The protein pulse feeding?

Increase of the dietary protein intake

**Spread protein diet**

**Pulse protein diet**

(Arnal et al. 1999, 2002
Bouillanne et al. 2013)
When Resynchronisation is inefficient?

- Increased Anabolic response Intensity
- Leucine signal
- Amino acid availability

Duration of the anabolic response?

- Interaction with protein and energy intake?
When Resynchronisation is inefficient? Whey too fast?

Amino acids

> 180 min

Muscle protein synthesis

< 180 min

Existence of « Stop Signals » stronger than the anabolic signals !!

Wilson et al. 2010; Atherton et al. 2010
What is the “Stop signal”?

**Muscle protein synthesis**

- Activity increases when ATP decreases
- Protein synthesis has a high energetic cost
- Protection mechanism?

**AMPK activity**

- < 180 min
- Activity increases when ATP decreases
- Protein synthesis has a high energetic cost
- Protection mechanism?
Nutritional strategy to take into account AMPK?

Prevent the AMPK activity to increase

Maintain the muscle ATP levels as long as possible during the post prandial period

Energy intake between 90 and 180 min after the beginning of the meal

[Graph showing muscle ATP levels over time]
Energetic chrononutrition?

**Muscle ATP**

- Meal with whey proteins
- Meal with whey proteins and energetic bolus 90 min later

**AMPK**

**Muscle protein synthesis**

- Meal with whey proteins
- Meal with whey proteins and energetic bolus 90 min later
Conclusions

- A nutritional strategy efficient in one situation of muscle wasting may not be efficient in another one
  - Intensity of the anabolic resistance
  - Duration of this anabolic resistance

- Leucine is indeed a very good stimulator for muscle protein synthesis

- If leucine given as a free amino acid over a normal protein diet
  - May be inefficient in several situations
  - Desynchronization with the other amino acids

- Synchronization of leucine with the other amino acids is possible with leucine rich proteins
  - Whey
**Dietary Whey supplementation: Matrix effect?**

**Process of the milk protein sources**

**Milk**

**Milk Gelation**

**Gelation** ➔ **Decreased digestion speed**
**Decreased of amino acid bioavailability**

Barbé et al., 2013
Matrix effect: Which consequences?

In normal healthy situations:
Processes has limited impact.

In anabolic resistance situations:
Processes blunt the anabolic effect of milk.

- Milk
- Acidic gelation
- Rennet gelation

Anabolic threshold
Conclusions

Prolonged and better efficiency of whey proteins if the anabolic threshold is also controlled

Combination whey and anti-inflammatory and antioxidants

So far, only the pulse protein feeding is efficient during aging

Feasibility? In other muscle loss situations?
Long term effect?

An energetic chrononutrition has to be tested in combination with whey proteins in (a) real muscle wasting situation(s)

Could the «Stop signal» be a target?
Presence of insulin resistance? (prevention of ATP to increase?)

Unknown is the effect of dietary chronic leucine bioavailability

Pro diabetic? Insulin resistance?
Thank you
Measurement of post prandial protein synthesis in steady state

Anabolic factors
(Amino acids)

Food intake

With free leucine into the diet

Little Food boluses